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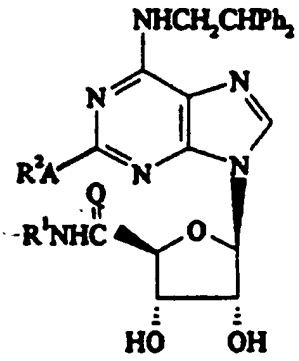
(54) Title: AMINO PURINE-β-D-RIBOFURANURONAMIDE DERIVATIVES

(57) Abstract

Amino purine-β-D-ribofuranuronamide derivatives are described having general formula (I) and salts and solvates thereof, wherein: R^1 is hydrogen, C_{3-8}cycloaklyl or C_{1-6}alkyl; A represents O, S, SO, SO_2, a saturated hydrocarbon moiety having from 1 to 4 carbon atoms or an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms; R^2 is C_{3-8}cycloalkyl, C_{3-8}cycloalkyl C_{1-6}alkyl, Alk_1Y, $-(CHR^5)_m$ $(Alk2)_nZ$ or appropriately substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl, and Q is oxygen or sulphur with the proviso that when A represents O, S, SO or SO_2, Alk_1 represents a C_{2-6}alkylene group. Compounds of formula (I) and their salts and solvates have use in medicine as anti-inflammatory agents, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.



(I)

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AMINO PURINE-β-D-RIBOFURANURONAMIDE DERIVATIVES

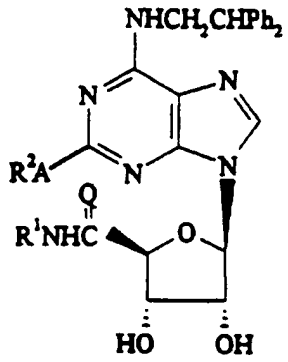
The present invention relates to therapeutically active amino purine-β-D-ribofuranuronamide derivatives, processes for the manufacture of said compounds, pharmaceutical formulations containing said compounds and the use of said compounds in chemotherapy. In particular, we have found a group of novel compounds which are effective in treating inflammatory diseases.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by circulating leukocytes binding to and extravasion through vascular endothelium. Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by gene expression in vascular endothelium in response to a variety of inflammatory mediators.

The primary function of leukocytes is to defend the host from invading organisms such as bacteria and parasites. Once a tissue is injured or infected a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment and resolution are not adequately controlled and the inflammatory reaction causes tissue destruction.

We have now found a novel group of compounds with broad anti-inflammatory properties which inhibit leukocyte recruitment and activation. The compounds are therefore of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation. The compounds of the invention may also represent a safer alternative to corticosteroids in the treatment of inflammatory diseases, whose uses are severely limited by their side-effect profiles.

Thus, according to on aspect of this invention, we provide a compound of general formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-8}cycloalkyl or C_{1-6}alkyl group;
A represents O, S, SO, SO_2, a saturated hydrocarbon moiety having from 1 to 4 carbon atoms or an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

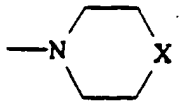
(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different

groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) $-Alk_1Y$ where Alk_1 is a C_{2-6} alkylene group or a bond and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or $arylC_{1-6}$alkyl) and

(viii) $-(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, $carboxyC_{1-4}$alkyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl,

with the proviso that when A represents O, S, SO or SO_2, Alk_1 represents a C_{2-6}alkylene group.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts such as acid addition salts derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates and maleates, and, if appropriate, inorganic base salts such as alkali metal salts, for example sodium salts. Other salts of the compounds of formula (I) include salts which are not physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. Examples of such salts include trifluoroacetates.

Examples of suitable solvates of the compounds of formula (I) include hydrates.

It will be appreciated that when R^2 in compounds of formula (I) contains one or more asymmetric carbon atoms and/or A represents SO (i.e. sulphur is an asymmetric centre), the invention includes all diastereoisomers of compounds of formula (I) and mixtures thereof. It will further be understood that carbon-carbon double bonds may exist in either cis or trans configuration and that all possible isomers are within the scope of the present invention. Otherwise, the stereochemical configuration of compounds of the invention is as depicted in formula (I) above.

It is to be understood that all tautomeric forms of the compounds of formula (I) are included within the scope of this invention.

The cycloalkyl group within R^1 or R^2 may be a monocyclic or bridged cyclic ring. Particular examples of suitable cycloalkyl ring systems include C_{3-8} monocyclic cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl. Within R^2 the C_{3-8} cycloalkyl group may particularly represent cyclopentyl or cyclohexyl.

The term 'aryl' as part of an arylC_{1-6}alkyl group may represent, for example, a phenyl group optionally substituted by one or more substituents (e.g. 1, 2 or 3 substituents) which may be the same or different and are selected from halogen, hydroxyl, C_{1-3}alkoxy and C_{1-3}alkyl.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group. Particular examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl.

The term 'alkylene' as part of a group means a straight or branched alkylene chain. Particular examples of suitable alkylene chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CHCH_3CH_2-$ and $-CH_2C(CH_3)_2CH_2-$.

When R^2 r presents a group $-Alk_1Y$ the C_{2-6}alkylen group may particularly represent $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2C(CH_3)_2CH_2-$.

When R^2 represents a group $-(CHR^5)_m(Alk_2)_nZ$ the chain $-(CHR^5)_m(Alk_2)_n-$ may particularly represent a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^5CHCH_3CH_2-$ or $-CHR^5CH_2-$ (where R^5 is a group CH_2R^6 and R^6 is as defined previously).

The term 'C_{2-7}acylamino' within R^2 means a C_{2-7}alkanoylamino group wherein the C_{1-6}alkyl portion thereof is a straight or branched alkyl group as previously defined and may be optionally substituted by one or more halogen atoms such as fluorine. Examples of suitable C_{2-7}alkanoylamino groups within R^2 include acetamido and trifluoroacetamido.

Within Z, the term 'pyridyl' means a 2-, 3- or 4-pyridyl group; the term 'pyrimidinyl' means a 2-, 4- or 5-pyrimidinyl group; the term 'imidazolyl' means a 1-,2-,4- or 5-imidazolyl group; and the term 'triazolyl' means a 1, 2, 4-triazolyl group (e.g. 1, 2, 4-triazol-l-yl or 1, 2, 4-triazol-3-yl).

R^1 preferably represents a C_{1-3}alkyl group, especially ethyl.

Compounds of formula (I) in which Q represents an oxygen atom are generally preferred.

When A represents a saturated or unsaturated hydrocarbon moiety, it may be straight or branched. When A represents an unsaturated hydrocarbon moiety it will contain at least one double or triple carbon-carbon bond.

Compounds of formula (I) in which $R^1NHC(=Q)-$ represents ethylaminocarbonyl are particularly preferred.

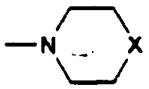
Compounds of formula (I) wherein A represents a sulphur atom or a saturated hydrocarbon moiety having from 1 to 4 carbon atoms or an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms are generally preferred. Particularly preferred compounds of formula (I) are compounds wherein A represents an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms.

A preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a substituted cyclopentyl or cyclohexyl group wherein the ring is substituted by one or two groups, especially one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido. Preferred substituents include hydroxy, NH_2 and dimethylamino.

A further preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents a pyrrolidin-3-yl or piperidin-3-yl group in which the ring nitrogen atom is substituted by hydrogen, C_{1-3}alkyl (e.g. ethyl) or benzyl.

Another preferred group of compounds of the invention are compounds of formula (I) in which R^2 represents $(CHR^5)_m(Alk_2)_nZ$ where R^5, m and n are as defined previously and Z is an optionally substituted imidazolyl, 1-pyrrolidinyl or 1-piperidinyl group. Particularly preferred are those compounds in which $-(CH_2R^5)_m(Alk_2)_n-$ represents $-CH_2CH_2-$.

Yet a further preferred group of compounds of the invention are compounds of formula (I) in which R^2 is Alk_1Y where Alk_1 is a C_{2-6}alkylene group and Y is C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O or CH_2).

It is to be understood that the present invention covers all combinations of particular and preferred groups referred to hereinabove.

Specific compounds of the present invention include:
1-[2-Cyclohexylthio-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamid ;

(cis)-1-[2-[(4-Aminocyclohexyl)thio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
1-[2-(3-Aminophenylthio)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)propyl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-E-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-Z-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[2-[2-(dimethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[2-[2-(diethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[2-[2-(diethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[2-[2-(dimethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
and physiologically acceptable salts and solvates thereof.

Preferred compounds of the present invention include 1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;
1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-E-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide; and physiologically acceptable salts and solvates thereof.

The potential for compounds of formula (I) to inhibit leukocyte function may be demonstrated, for example, by their ability to inhibit superoxide (O_2^-) generation from neutrophils stimulated with chemoattractants such as N-formylmethionyl-leucyl-phenylalanine (fMLP). Accordingly, compounds of formula (I) are of potential therapeutic benefit in providing protection from leukocyte-induced tissue damage in diseases where leukocytes are implicated at the site of inflammation.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as adult respiratory distress syndrome (ARDS), bronchitis (including chronic bronchitis), cystic fibrosis, asthma (including allergen-induced asthmatic reactions), emphysema, rhinitis and septic shock. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), Helicobacter-pylori induced gastritis and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, and non-steroidal anti-inflammatory drug-induced gastropathy. Furthermore, compounds of the invention may be used to treat skin diseases such as psoriasis, allergic dermatitis and hypersensitivity reactions.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiac conditions such as peripheral vascular disease, post-ischaemic reperfusion injury and idiopathic hypereosinophilic syndrome.

Compounds of the invention which inhibit lymphocyte function also have use in the treatment of auto-immune diseases such as rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition who is susceptible to leukocyte-induced tissue damage, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for us in anti-inflammatory therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate ther of

together, if desirable, with one or more physiologically acceptable carriers or excipients.

The compounds according to the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration, preferably for parenteral or topical (e.g. by aerosol) administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator, solutions for nebulisation or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqu ous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Capsules and cartridges of for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents such as corticosteroids or NSAIDs.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example an anti-inflammatory agent such as a corticosteroid or NSAID.

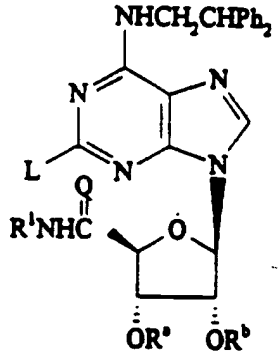
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier th reof repres nt a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.01 to 500mg/kg body weight, preferably 0.01 to 100mg/kg body weight, 1 to 4 times daily. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention. In the following procedures, the groups R^1, R^2 and Q are as defined for compounds of formula (I) unless otherwise stated.

Thus, according to a first process, a compound of formula (I) wherein A represents S may be prepared by treating a compound of formula (II)



(II)

(wherein L represents halo such as iodo, bromo or chloro and R^a and R^b each represent a hydrogen atom or together form an alkylidene group such as isopropylidene) with a thiol $R^{2a}SH$ or, preferably, a thiolate anion $R^{2a}S^-$ (wherein R^{2a} is a group R^2 or is a protected derivative thereof) followed, where necessary, by the removal of any protecting groups present.

The displacement reaction to introduce the sulphur moiety may be carried out by heating the reagents at a temperature in th range of 20 to 150°C,

preferably 20° to 100°C,optionally in the presence of a solvent such as dimethylsulphoxide or N,N-dimethylformamide.

The thiolate anion can be generated by treatment of the corresponding thiol $R^{2a}SH$ with a suitable base such as an alkali metal hydride, e.g. sodium hydride, or an alkali metal carbonate, e.g. potassium carbonate or an amine, e.g. triethylamine. Alternatively, the thiolate may be generated from the corresponding thiol ester $R^{2a}SC(O)R^c$ (where R^c is alkyl) by treatment with a suitable base such as an alkali metal hydroxide, e.g. sodium hydroxide.

Compounds of formula (I) wherein A represents SO or SO_2 may be prepared from the corresponding compounds of formula (I) wherein A represents S by oxidation using conventional procedures.

Compounds of formula (I) wherein A represents an oxygen atom may be prepared by reaction of a compound of formula (II) with an alkoxide $R^{2a}O^-$ (wherein R^{2a} is as previously defined) followed, where necessary, by removal of any protecting groups present.

The displacement reaction may be carried out in a similar way to that for the preparation of compounds of formula (I) wherein A is S. The alkoxide may be generated by treatment of the corresponding alcohol $R^{2a}OH$ with a suitable base such as, for example, butyllithium or an alkali metal hydride e.g. sodium hydride. Suitable reagents and conditions will be readily apparent to those skilled in the art, see, for example, "The Chemistry of the Ether Linkage", Patai, Interscience Publishers, New York, 1967.

Compounds of formula (I) wherein A represents an acetylene moiety may be prepared from compounds of formula (II) by reaction with a terminal acetylene $R^{2a}A^aH$ (wherein R^{2a} is as previously defined, A^a represents a C_{1-4} hydrocarbon moiety and R^2A^aH contains a terminal triple bond) in the presence of a palladium (O) catalyst, followed where necessary, by removal of any protecting groups present.

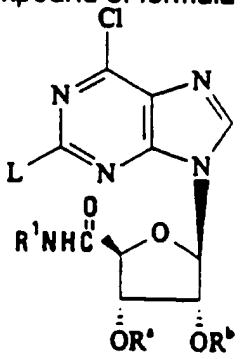
Compounds of formula (I) wherein A represents an alkyl or alkenyl moiety may be prepared from compounds of formula (I) described herein where A represents an acetylene moiety by reduction using conventional methods.

Alternatively, compounds of formula (I) wherein A represents an alkyl or alkenyl moiety may be prepared from compounds of formula (II) by reaction with an reagent such as a suitable tetraalkylstannane derivative in the presence of a palladium (0) catalyst, followed where necessary by removal of any protecting groups present.

A compound of formula (II) in which Q represents a sulphur atom may be prepared from a compound of formula (II) in which Q represents an oxygen atom and R^a and R^b together form an alkylidene group such as isopropylidene by thianation followed, if appropriate, by the removal of the alkylidene group.

The thianation reaction may be conveniently effected using known thianation agents such as hydrogen sulphide, phosphorus pentasulphide or Lawesson's reagent (p-methoxyphenylthiophosphine sulphide dimer). The reaction may be carried out in a known manner. For example when hydrogen sulphide is used an acid such as hydrochloric acid may conveniently be added in catalytic amounts and the reaction carried out in a polar solvent such as acetic acid or ethanol. When using Lawesson's reagent, the reaction may conveniently be carried out in a dry solvent such as toluene or methylene chloride.

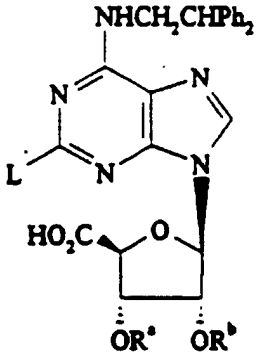
A compound of formula (II) in which Q represents an oxygen atom may be prepared by treating a compound of formula (III)



(III)

(wherein R^a and R^b are as defined previously) with 2,2-diphenylethylamine, preferably in the presence of a base such as an amine base (e.g. diisopropylethylamine) and in a solvent such as an alcohol (e.g. isopropanol) at an elevated temperature (e.g. reflux), followed if desired by removing any protecting groups present.

A compound of formula (II) in which Q represents an oxygen atom may also be prepared by treating a compound of formula (IV)

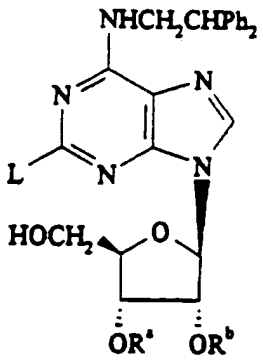


(IV)

(wherein R^a and R^b are as defined previously) or an active derivative thereof such as the corresponding acid halide with an amine R^1NH_2, followed if desired by removing any protecting groups present.

The amination reaction may be effected in a known manner, for example by adding the amine in a solvent such as a halogenated hydrocarbon (e.g. methylene chloride) at about 0^0 to 20^0C to the compound (IV) or, more particularly, the corresponding acid chloride. The acid chloride may be prepared by treating compound (IV) with thionyl chloride, conveniently at an elevated temperature.

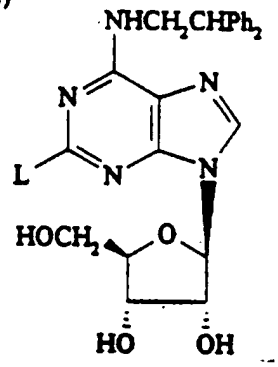
A compound of formula (IV) may be prepared by oxidising a compound of formula (V)



(V)

or a salt thereof (wherein R^a and R^b together form an alkylidene group such as isopropylidene), followed if desired by removing the alkylidene group. The oxidation reaction may be effected in a known manner using an oxidising agent such as potassium permanganate or pyridinium dichromate.

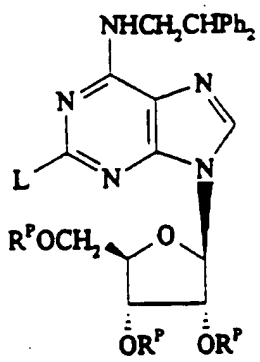
A compound of formula (V) wherein R^a and R^b together form an alkylidene group, such as isopropylidene, or a salt thereof may be prepared by treating a compound of formula (VI)



(VI)

with a ketone such as acetone and/or with 2,2-dimethoxypropane in the presence of an acid, for example p-toluenesulphonic acid, conveniently at about room temperature.

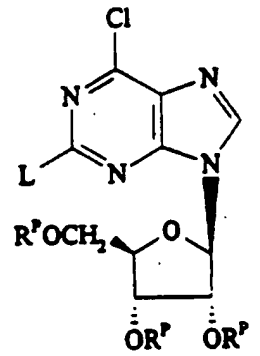
A compound of formula (VI) may be prepared by deprotecting a compound of formula (VII)



(VII)

(wherein R^P is a suitable hydroxyl protecting group). Suitable methods of deprotection are described hereinafter.

A compound of formula (VII) may be prepared by treating a compound of formula (VIII)



(VIII)

(wherein R^P is as defined previously) with 2,2-diphenylethylamine under the conditions described previously for preparing compounds of formula (II) from compounds of formula (III).

The compounds of formulae (III) and (VIII) are either known compounds or may be prepared by methods analogous to those described in the art for preparing the known compounds of formulae (III) and (VIII).

Compounds of the above formulae wherein L represents Br or I may be prepared from the corresponding compounds wherein L represents Cl by reaction with hydrazine followed by reduction, for example using Raney Nickel, to the corresponding amine, and subsequent reaction with an organohalogen compound such as bromoform or diiodomethan in the presence of copper (I) bromide or iodide, optionally in the presence of one or more other halogen

sources such as halide salts or the appropriate free halogen and a diazotising agent, such as potassium nitrite or t-butyl nitrite.

The thiols $R^{2a}SH$, thio esters $R^{2a}SC(O)R^c$, alcohols $R^{2a}OH$ and acetylenes $R^{2a}A^aH$ are either known in the art or may be prepared by the methods described in the Examples Section hereinafter or by methods analogous to such methods hereinafter.

Compounds of formulae (II) and (IV) are novel intermediates and represent further aspects of the present invention. Compounds of formula (II) in which R^a and R^b represent hydrogen atoms are also active compounds in their own right and constitute a further particular aspect of the present invention.

It will be appreciated that in addition to 2',3'-diol groups, groups present within R^2 may need to be protected, and deprotection may be required as an intermediate or final step to yield the desired compound. Thus, according to another general process (B), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) to reaction to remove the protecting group or groups. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) or sulphonyl (e.g. allylsulphonyl or tosyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene and P.G. M. Wuts (John Wiley and Sons, 1991). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conv ntional techniques. Thus, for example alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, .g. by hydrolysis under

acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride. Carboxyl protecting groups may conveniently be represented by appropriate hydroxyl protecting groups above with deprotection effected according to the methods described above. An example of such a group is an alkyl (e.g. methyl or t-butyl) group which can be removed by acid hydrolysis (e.g. using trifluoroacetic or hydrochloric acid) or an aralkyl (e.g. benzyl) group which can be removed by catalytic hydrogenolysis.

Particularly suitable hydroxyl protecting groups represented by R^P include acyl groups such as acetyl or benzoyl. An alkylidene protecting group may conveniently be removed by acid-catalysed hydrolysis, for example using trifluoroacetic, sulphuric or hydrochloric acid.

Compounds of formula (I) may also be prepared from other compounds of formula (I) or protected derivatives thereof using conventional interconversion procedures, including N-acylation, N-debenzylation, partial or complete hydrogenation of an unsaturated carbon-carbon bond and oxidation of a hydroxyl group to a ketone, followed, if necessary, by the removal of any protecting groups present.

Individual isomers of formula (I) may either be prepared from starting materials having the desired stereochemistry or by epimerisation, resolution or chromatography (e.g. HPLC separation) at an appropriate stage in the synthesis of the required compounds of formula (I) using conventional means.

When it is desired to prepare an acid addition salt of a compound of formula (I) the product of the above procedure may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) in the form of a free

base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol, ethanol or isopropanol).

Inorganic basic salts may be prepared by reacting the free base of a compound of formula (I) using conventional methods.

Solvates (e.g. hydrates) of a compound of formula (I) may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C. Hereinafter the term DMSO means dimethylsulphoxide. DMF means N,N-dimethylformamide.

EXAMPLES

General

Where products were purified by column chromatography, 'silica' refers to silica gel for chromatography, 0.063 to 0.20mm mesh (e.g. Merck Art 7735); 'flash silica' refers to silica gel for chromatography, 0.040 to 0.063mm mesh (e.g. Merck Art 9385). In this latter case column elution was accelerated by an applied pressure of nitrogen at up to 10 p.s.i.

INTERMEDIATE 1

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-triacetate

A solution of 2,6-dichloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine[1] (6.68g) in 2-propanol (300ml) was stirred and heated at reflux with 2,2-diphenylethylamine (4.3g) in the presence of diisopropylethylamine (3.8ml) for 3.5h. The cooled mixture was reduced in volume by evaporation in vacuo and the residue was diluted with ethyl acetate (200ml). This mixture was washed with water (100ml), 10% citric acid solution (2x100ml) and water (100ml) then dried ($MgSO_4$) and vaporated to give the title compound (9.01g) as a pale yellow froth. A sample (500 mg) was purified by column chromatography on

flash silica eluting with ethyl acetate:cyclohexane (1:2). The product (0.34g) was obtained as a white froth. $[a]_D$ -20° ($CHCl_3$ c=1%).

1. M.J.Robins and B.Uznanski, Canad.J.Chem., 1981, 59(17), 2608.

INTERMEDIATE 2

2-Chloro-N-(2,2-diphenylethyl)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-triacetate (2.0g) was dissolved in methanol (120ml) and the solution was stirred at room temperature with 2M aqueous sodium carbonate solution (10ml). After 2h the mixture was diluted with water (350ml) and extracted with ethyl acetate (2x100ml). The extract was washed with water (100ml) and dried ($MgSO_4$) then evaporated to leave a froth (1.42g). A sample (0.42g) was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane (3:1). Evaporation of appropriate fractions gave an oil which was treated with ether (20 ml) to give a solid, which was collected by filtration, washed with ether and dried in vacuo to give the title compound (0.177g) as a solid. $[a]_D$ -39° ($CHCl_3$ c=1%).

INTERMEDIATE 3

2-Chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine toluene-4-sulphonate salt

Toluene-4-sulphonic acid (7.0g) was added to a stirred solution of 2-chloro-N-(2,2-diphenylethyl)-adenosine (6.85g) in acetone (300ml) and 2,2-dimethoxypropane (90ml). After a few minutes a precipitate formed which dissolved within 0.5h. The reaction was stirred for 3 days and the precipitate formed was collected by filtration and washed with acetone (50ml) and dried to give the title compound (4.64g). $[a]_D$ -38° (1,4-dioxan c=1%). A second crop (2.7g) was obtained from the mother liquors.

INTERMEDIATE 4

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid

A solution of 2-chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine toluene-4-sulphonate salt (6.94g) in 1,4-dioxan (200ml) was added to a cold (4°C) solution of potassium permanganate (8.85g,56.1mmol) and potassium hydroxide (2.71g) in water (200ml) keeping the temperature below

10°C. On complete addition the mixture was stirred for 3.5h between 5°C and room temperature. A 5% aqueous solution of sodium metabisulphite was added in portions until all colouration had been discharged. The pH was then adjusted to pH 3 with concentrated hydrochloric acid and the mixture was extracted with ethyl acetate (3x200ml). The extract was washed with water (200ml) and dried ($MgSO_4$) and evaporated to leave a waxy solid (5.45g) which was dried in vacuo. The majority of this solid (4.1g) was stirred with ether (100ml) and 5% aqueous sodium bicarbonate solution (100ml) until solution was obtained. The aqueous phase was washed with ether (2x100ml) then brought to pH3 with 10% citric acid solution to give a precipitate which was collected by filtration, washed with water (100ml) and dried. The resulting solid (6.1g) was stirred with water (500ml) for 2h then collected by filtration, washed with water (50ml) and dried in vacuo over phosphorus pentoxide to give the title compound (3.52g) $[a]_D$ +53° ($CHCl_3$ c=1%).

INTERMEDIATE 5

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid (3.3g) in thionyl chloride (10ml) was heated at 70°C for 1.5h. The mixture was evaporated to leave a pale brown froth which was azeotroped with toluene twice. The resulting froth was dissolved in dichloromethane (50ml) and the solution was cooled to 5°C. A solution of ethylamine (6ml) in dichloromethane (20ml) was added in portions and the mixture was left at 5°C for 30 min then poured into water (100ml). The aqueous phase was extracted with dichloromethane (3x50ml), the extract was washed with water and dried ($MgSO_4$) then evaporated to leave a froth (3.37g) which was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane (1:1) to give the title compound (2.74g) as a pale yellow froth. $[a]_D$ -18.9° ($CHCl_3$ c=0.9%).

INTERMEDIATE 6

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-tribenzoate

A mixture of 2,6-dichloro-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-9H-purine[1] (67.69g), 2,2-diphenylethylamine (27.67g) and diisopropylethylamine (75.5g) in

2-propanol (2200ml) was heated under reflux for 2.5h. The cooled mixture was evaporated, and the residual orange foam purified on flash silica (1.5 kg) eluting with ethyl acetate:cyclohexane (1:2) to yield the title compound (71.2g) as a pale brown foam. ^{1}H nmr δ ($CDCl_3$) 4.2 to 4.4 and 4.6 to 4.95 (2m,6H), 5.97 (br.s,1H),6.14 (q,2H), 6.43 (d,1H), 7.15 to 7.65 (m, ca 19H), 7.79 (s,1H), 7.9 to 8.15 (m,6H).

1. K.Imai, et al., Chem. Pharm. Bull., 1966, 14, 1377.

INTERMEDIATE 7

Alternative preparation of:

2-Chloro-N-(2,2-diphenylethyl)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine 2',3',5'-tribenzoate (71.2g) in methanol (980ml) was treated with potassium carbonate (52.1g). The suspension was stirred at 22°C for 2h. It was then acidified to pH 8 with concentrated hydrochloric acid, evaporated and purified on flash silica (2kg) eluting with dichloromethane:ethanol:0.880 ammonia (90:10:1) to give the title compound (40.2g) as a white solid. ^{1}H nmr δ (DMSO-d_6) 3.58 (m,1H), 3.65 (m,1H), 3.84 (br.s,1H), 4.0 to 4.2 and 4.4 to 4.65 (2m,5H), 5.04 (t,1H), 5.22 (d,1H), 5.48 (d,1H), 5.82 (m,1H), 7.1 to 7.4 (m,10H), 8.33 (s,1H), 8.42 (t,1H).

INTERMEDIATE 8

2-Chloro-N-(2,2-diphenylethyl)-2,3-O-(1-methylethylidene)-adenosine

2-Chloro-N-(2,2-diphenylethyl)-adenosine (40g) in acetone (970ml) was treated with 2,2-dimethoxypropane (49ml) and toluene-4-sulphonic acid (4.97g). The mixture was stirred at ca 22°C for 67h, then the slurry was evaporated and chromatographed on flash silica eluting with dichloromethane:methanol (19:1) to give the title compound (39.6g) as a white solid. A portion (1.5g) was recrystallised from ethyl acetate to give an analytically pure sample (1.27g). m.p. 185 to 187°; $[a]_D$ -86°(c,0.8%, $CHCl_3$).

INTERMEDIATE 9

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

1-(2,6-Dichloro-9H-purin-9-yl)-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide[1] (5.66g) was heated at reflux in 2-propanol (300ml) with

2,2-diphenylethylamine (3.62g) in the presence of N,N-diisopropylethylamine (13.2ml) for 6h. The cooled solution was evaporated to a brown foam which was purified on silica eluting with ethyl acetate to give the title compound (7.31g) as a pale yellow foam. ^{1}H nmr δ (DMSO-d6) 0.62(t,3H), 1.34(s,3H), 1.53(s,3H), 2.82(m,2H), 4.05(m,1.5H), 4.54(m,2.5H), 5.40(m,2H), 6.18(s,1H), 7.1 to 7.4(m,10H), 7.50(t,1H), 8.22(s,1H), 8.40(m,1H).

1. R.R.Schmidt et al., Chem.Ber., 1980, 113, 2891.

INTERMEDIATE 10

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (2.02g) was treated with trifluoroacetic acid (10ml) and water (1.1ml), and the resulting solution was stirred at 20°C for 2h. The mixture was evaporated and the residue was treated with sodium hydrogen carbonate (3.75g) and ethanol (30ml) and stirred for 1h. The mixture was filtered and the solid was washed with ethanol. The total filtrate and washings were evaporated and the residue was purified on flash silica eluting with ethyl acetate:methanol (19:1) to give the title compound (1.96g) as a white solid. ^{1}H nmr δ (DMSO-d6) 1.05(t,3H), 3.22(m,2H), 4.0 to 4.2(m,2.5H), 4.30(m,1H), 4.45 to 4.65(m,2.5H), 5.58(d,1H), 5.72(d,1H), 5.90(d,1H), 7.14 to 7.40(m,10H), 8.36(t,1H), 8.43(s,1H), 8.52(t,1H).

INTERMEDIATE 11

(trans)-(4-Hydroxycyclohexyl)carbamic acid 1,1-dimethylethyl ester

(trans)-4-Aminocyclohexanol (13.2g) was dissolved in dioxan (100ml) and water (30ml) and treated with di-*tert*-butyl dicarbonate (19g) and sodium carbonate (27.7g). The reaction mixture was stirred at room temperature for 16h and then partitioned between ethyl acetate (500ml) and water (500ml). The aqueous phase was extracted with ethyl acetate (2x250ml) and the combined organic extracts washed with water (2 x 250ml). The organic phase was dried ($MgSO_4$) and evaporated to give a white solid. Trituration with cyclohexane (100ml) afforded the title compound as a white solid (16.1g). ^{1}H nmr δ (DMSO-d_6) includes 1.03-1.25 (m, 4H), 1.38 (s, 9H), 1.63 - 1.86 (m, 4H), 3.13 (m, 1H), 4.48 (d, 1H), 6.63 (brd, 1H).

INTERMEDIATE 12

(trans)-[4-[(Methylsulfonyl)oxy]cyclohexyl]carbamic acid 1,1-dimethylethyl ester

A solution of methanesulfonyl chloride (2.67ml) in dichloromethane was added dropwise over 0.5h to a stirred solution of (trans)-(4-hydroxycyclohexyl)carbamic acid 1,1-dimethylethyl ester (6.2g) and triethylamine (6.02ml) in dichloromethane (120ml) at 0-5° under nitrogen. After stirring at 0-5° for 1h, the reaction mixture was washed with water (2x200ml). The organic phase was dried ($MgSO_4$) and evaporated to give the title compound as a white solid (8.42g). ^1H nmr δ ($CDCl_3$) includes 1.17 - 1.36 (m, 2H), 1.44 (s, 9H), 1.59 - 1.78 (m, 2H), 2.01 - 2.21 (m, 4H), 3.01 (s, 3H), 3.47 (m, 1H), 4.37 (brs, 1H), 4.62 (m, 1H).

INTERMEDIATE 13

(cis)-[4-(Acetylthio)cyclohexyl]carbamic acid 1,1-dimethylethyl ester

A stirred solution of (trans)-[4-[(methylsulfonyl)oxy]cyclohexyl]carbamic acid 1,1-dimethylethyl ester (570mg) in DMF (10ml) was treated with potassium thioacetate (333mg) and heated at 70° for 24h. On cooling, the reaction mixture was diluted with ethyl acetate (150ml) and washed with water (3x150ml) and brine (50ml). The organic solution was dried (Na_2SO_4) and evaporated to give a dark brown gum which was purified on flash silica. Elution with ethanol:chloroform (1:200 →1:100) afforded the title compound as a dark brown solid (156mg). ^1H nmr δ ($CDCl_3$) includes 1.34-1.54 (m, 2H), 1.44 (s, 9H), 1.66-1.91 (m, 6H), 2.31 (s, 3H), 3.53 (m, 1H), 3.74 (m, 1H), 4.47 (brs, 1H).

INTERMEDIATE 14

2-Amino-N-(2,2-diphenylethyl)-adenosine

To a stirring suspension of guanosine hydrate (0.500g), and 2,2-diphenylethylamine (0.982g) in p-xylene (3ml) at room temperature, was added 1,1,1,3,3,3-hexamethyldisilazane (1.39ml) followed by trimethylsilyl trifluoromethanesulfonate (0.03ml). The mixture was stirred at room temperature for t n minutes, then put into an oil bath at 150°C, and the resulting clear pale yellow solution was heated at ~130°C for forty hours, then allowed to cool to room temperatur . To this was then added methanol (10ml) followed by

tetrabutylammonium fluoride (5 drops of a 1M solution in tetrahydrofuran), and the resulting mixture was heated at reflux for 1.5 hours. Flash silica (3g) was added and the mixture concentrated to dryness then purified by column chromatography on flash silica eluting with ethyl acetate:industrial methylated spirits:acetic acid (90:10:1) to give the title compound (0.460g) as a foam. ^{1}H nmr δ (DMSO-d_6) includes 3.54 (dd,1H), 3.64 (dd,1H), 3.89-3.94 (m,1H), 4.00-4.12 (m,3H), 4.51 (t,1H), 4.56-4.64 (hump,1H), 5.72 (d,1H), 5.88-5.95 (bs,2H), 7.15-7.38 (m,10H), 7.85-7.89 (bs, 1H).

INTERMEDIATE 15

2-Amino-N-(2,2-diphenylethyl)-2',3'-O-(1-methylethylidene)-adenosine

Toluene-4-sulphonic acid monohydrate (5.9g) was added to a stirred solution of 2-amino-N-(2,2-diphenylethyl)-adenosine (13.05g) in acetone (100ml) and 2,2-dimethoxypropane (35ml). The pale yellow solution was stirred at room temperature for 21 hours, then concentrated to give a pale brown foam. This was dissolved in ethyl acetate (150ml) and washed successively with saturated aqueous sodium hydrogen carbonate (150ml) and brine (150ml), then dried ($MgSO_4$), and concentrated to give a light brown solid. This solid was purified by column chromatography on flash silica eluting with ethyl acetate, to give the title compound (13.43g) as a pale yellow foam. ^{1}H nmr δ ($CDCl_3$) includes 1.38 (s,3H), 1.63 (s,3H), 4.14-4.24 (m,2H), 4.29-4.39 (m,1H), 4.49 (s,1H), 4.77(bs,2H), 5.08 (d,1H), 5.19 (t,1H), 5.70 (d,1H), 7.19-7.34 (m,10H), 7.40 (s,1H).

INTERMEDIATE 16

1-[2-Amino-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid

A solution of 2-amino-N-(2,2-diphenylethyl)-2',3'-O-(1-methylethylidene)-adenosine (30.03g) in 1,4-dioxan (130ml) was added slowly to a cold (4°C) solution of potassium permanganate (42.51g) and potassium hydroxide (10.06g) in water (260ml) and 1,4-dioxan (130ml). The mixture was stirred at 4°C for thirty minutes, then at room temperature for a further four hours. The mixture was then filtered through a pad of celite, and the residue washed with 1,4-dioxan and water (1:1, 100ml). The purple filtrate was treated with sodium

metabisulphite (~2g) and the resulting white precipitate was filtered off. The pH of this second filtrate was then adjusted to 5.5 with concentrated hydrochloric acid and the mixture extracted with ethyl acetate (1x1000ml),(1x500ml). The combined extracts were dried ($MgSO_4$) and concentrated to give a brown foam (28.9g). This was purified by column chromatography on flash silica eluting with dichloromethane:methanol (25:1) to give the title compound (12.61g) as a pale yellow solid. ^1H nmr δ (DMSO-d_6) includes 1.34 (s,3H), 1.50 (s,3H), 3.95-4.10 (hump, 2H), 4.50-4.63 (m,2H), 5.30 (d,1H), 5.55 (dd,1H), 5.90-6.00 (hump,2H), 6.11 (s,1H), 7.10-7.40 (m,10H), 7.78 (bs,1H).

INTERMEDIATE 17

1-[2-Amino-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

A solution of 1-[2-amino-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-2,3-O-(1-methylethylidene)-β-D-ribofuranuronic acid (4.1g) in thionyl chloride (11.8ml) was heated at 75°C for two hours. The mixture was evaporated to leave a yellow/brown solid which was azeotroped with toluene three times. The resulting solid was dissolved in dichloromethane (30ml) and the solution cooled to 4°C. A solution of ethylamine (40ml) in dichloromethane (10ml) was added slowly over 30 minutes and the mixture was left at 4°C for one hour then poured into water (50ml). The aqueous phase was extracted with dichloromethane (1x100ml),(3x50ml), the extracts were combined, washed with brine (100ml) and dried ($MgSO_4$) then evaporated to leave a solid which was purified by column chromatography on flash silica eluting with dichloromethane:methanol (20:1) to give the title compound (3.58g) as a yellow solid. ^1H nmr δ (DMSO-d_6) includes 0.69 (t,3H), 1.32 (s,3H), 1.51 (s,3H), 2.80-2.92 (m,2H), 3.90-4.10 (hump,2H), 4.45 (d,1H), 4.50-4.62 (m,1H), 5.29 (d,1H), 5.40 (d,1H), 5.90-6.00 (hump,2H), 6.12 (s,1H), 7.10-7.40 (m,10H), 7.79 (bs,1H).

INTERMEDIATE 18

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamid-

t-Butyl nitrite (2.98ml) was added portionwise to a stirring mixture of 1-[2-amino-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (3.4g), iodine (1.59g),

copper(I)iodide (0.69g) and diiodomethane (6.31ml) in tetrahydrofuran (110ml). The mixture was heated at reflux for 3 hours then allowed to cool to room temperature. The brown mixture was treated with saturated aqueous ammonium chloride (200ml) and dichloromethane (100ml) and stirred vigorously. To this was added .880 ammonia solution dropwise until a blue colour of the ammonia complex was observed. The two layers were separated and the aqueous was further extracted with dichloromethane (3x150ml). The extracts were combined, dried ($MgSO_4$) and concentrated to give a dark brown oil. This oil was purified by column chromatography on flash silica eluting with ethyl acetate:cyclohexane ((0:1),(2:1)) to give the title compound (1.45g) as a yellow solid. ^1H nmr δ (DMSO-d_6) includes 0.61 (t,3H), 1.38 (s,3H), 1.55 (s,3H), 2.70-2.82 (m,2H), 4.32-4.42 (m,2H), 4.50-4.57 (m,1H), 4.61 (s,1H), 4.91 (d,2H), 6.47 (s,1H), 7.10-7.35 (m,10H), 8.61 (s,1H).

INTERMEDIATE 19

3-(Piperidin-1-yl)propyne

Propargyl bromide (34.92g) was added dropwise to a stirred solution of N,N-diisopropylethylamine (102.2ml) and piperidine hydrochloride (25.0g) in diethyl ether (210ml), and the mixture then heated to reflux for 24 hours. The mixture was allowed to cool to room temperature, filtered, and the filtrate concentrated to give a dark brown slurry. This oil was purified by column chromatography on flash silica eluting with dichloromethane:methanol (9:1) to give the title product (4.89g) as a pungent dark brown oil. ^1H nmr δ (DMSO-d_6) includes 1.30-1.41 (m,2H), 1.45-1.55 (m,4H), 2.39 (t,4H), 3.09 (t,1H), 3.20 (d,2H).

INTERMEDIATE 20

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-hydrazino-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

Hydrazine hydrate (8ml) and water (1ml) were added to a stirred mixture of 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (2.18g) in absolute ethanol (10ml), and the mixture heated at ~60°C for 5.5 hours. Further absolute ethanol (4ml) was added and heating continued for a further hour, th n the reaction mixture was allowed to cool to room temperature and left to stand for 40 hours. Ethyl acetate (100ml) and water (100ml) were added, the phases separated, and the

aqueous further extracted with ethyl acetate (100ml). The extracts were combined, dried ($MgSO_4$), and concentrated to give a white solid. This was redissolved in absolute ethanol (20ml) , treated with hydrazine hydrate (18ml) and heated at ~55°C for a total of fourteen hours. The mixture was then allowed to cool, diluted with water (30ml), left to stand for one hour, then the white solid filtered off. This white solid was washed with water, then dried under vacuum for four days to give the title compound (1.970g) as a white solid. ^1H nmr δ (DMSO-d_6) includes 0.42 (t,3H), 1.37 (s,3H), 1.50 (s,3H), 2.53-2.80 (m,2H), 3.80-4.20 (m,3H), 4.50 (s,1H), 4.52-4.62 (m,1H), 5.32 (d,1H), 5.68 (d,1H), 6.28 (bs,1H), 7.10-7.33 (m,12H), 7.49 (bs,1H), 7.80 (bs,1H).

INTERMEDIATE 21

1-[2-Amino-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

Raney nickel (~four spoonfuls) was treated with absolute ethanol (15ml) under nitrogen, the solid allowed to settle, then the ethanol pipetted off into a solution of aqueous hydrochloric acid (6M). This was repeated twice. To this Raney nickel was then added 1-[6-[(2,2-diphenylethyl)amino]-2-hydrazino-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (1.927g) as a solution in absolute ethanol (120ml). The mixture was purged five times with nitrogen, then five times with hydrogen, then stirred overnight in an atmosphere of hydrogen. The mixture was then purged five times with nitrogen, filtered through a pad of celite under nitrogen, the residue washed with ethanol (~1000ml), and the filtrate and washings then combined and evaporated to give the title compound (1.506g) as a yellow/green solid. ^1H nmr δ (DMSO-d_6) includes 0.69 (t,3H), 1.33 (s,3H), 1.51 (s,3H), 2.80-2.95 (m,2H), 3.90-4.10 (hump,2H), 4.45 (d,1H), 4.50-4.62 (m,1H), 5.28 (d,1H), 5.40 (d,1H), 5.91 (bs,2H), 6.12 (s,1H), 7.10-7.40 (m,10H), 7.78 (bs,1H).

INTERMEDIATE 22

[3-Z-(Piperidin-1-yl)-1-propen-1-yl]tri-*n*-butyltin

A stirring mixture of 3-(piperidin-1-yl)propyne (0.180g) and tri-*n*-butyltin hydride (0.511g) was left at room temperature for 24 hours, then heated at ~80°C for a

further 24 hours. The mixture was allowed to cool then purified by column chromatography on flash silica eluting with cyclohexane:ethyl acetate (5:1) to give the title product (0.055g) as a yellow liquid. ^{1}H nmr δ ($CDCl_3$) includes 0.85-1.05 (m,15H), 1.25-1.70 (m,18H), 2.30-2.42 (bs,4H), 2.96 (d,2H), 6.00 (d,1H), 6.53-6.65 (m,1H).

INTERMEDIATE 23

Acetic acid 2-(piperidin-1-yl)ethylthio ester

A mixture of N-(2-chloroethyl)piperidine hydrochloride (1.84g) and potassium thioacetate (1.14g) in DMF (30ml) was stirred under nitrogen for 3 days. A solution of saturated sodium bicarbonate (20ml) and water (200ml) were added and the mixture was extracted with ethyl acetate (100ml, 2 x 50ml). The extract was washed with water (100ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluted with 5% methanol in dichloromethane to give the title compound (1.25g) as a deep red oil. ^{1}H nmr δ ($CDCl_3$) includes 1.4 (m,2H), 1.55 (m,4H), 2.3 (s,3H), 2.45 (m,4H), 2.5 (t,2H), 3.0 (t,2H).

INTERMEDIATE 24

Acetic acid 2-(pyrrolidin-1-yl)ethylthio ester

A mixture of N-(2-chloroethyl)pyrrolidine hydrochloride (2.3g) and potassium thioacetate (3.4g) in DMF (15ml) was stirred under nitrogen for 24h. A 1M solution of sodium carbonate (40ml) was added and the mixture was extracted with ethyl acetate (2 x 50ml). The extract was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluted with 5% methanol in dichloromethane to give the title compound (0.503g) as a deep red oil. ^{1}H nmr δ ($CDCl_3$) includes 1.8 (m,4H), 2.35 (s,3H), 2.55 (m,4H), 2.65 (t,2H), 3.05 (t,2H).

INTERMEDIATE 25

Acetic acid 2-(diethylamino)ethylthio ester

A mixture of N-(2-chloroethyl)diethylamine hydrochloride (3.44g) and potassium thioacetate (2.28g) in DMF (20ml) was stirred under nitrogen for 24h. A 1M solution of sodium carbonate (40ml) was added and the mixture was extracted

with ethyl acetate (50ml, 30ml). The extract was washed with water (50ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluted with 5% methanol in dichloromethane to give the title compound (1.14g) as a deep red oil. ^1H nmr δ ($CDCl_3$) includes 1.05 (t,6H), 2.35 (s,3H), 2.57 (q,4H), 2.63 (t,2H), 2.97 (t,2H).

INTERMEDIATE 26

Acetic acid 2-(dimethylamino)ethylthio ester

A mixture of N-(2-chloroethyl)dimethylamine hydrochloride (2.88g) and potassium thioacetate (2.28g) in DMF (20ml) was stirred under nitrogen for 24h. A 1M solution of sodium carbonate (40ml) was added and the mixture was extracted with ethyl acetate (2 x 50ml). The extract was washed with water (30ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluted with 5% methanol in dichloromethane to give the title compound (0.446g) as a deep red oil. ^1H nmr δ ($CDCl_3$) includes 2.25 (s,6H), 2.35 (s,3H), 2.48 (t,2H), 3.03 (t,2H).

INTERMEDIATE 27

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (Intermediate 18, 0.200g) was treated with trifluoroacetic acid (1.8ml) followed by water (0.2ml), and stirred at room temperature for 45 minutes. The mixture was concentrated to a yellow oil which was treated with absolute ethanol (10ml) and sodium hydrogen carbonate (1.00g), and the heterogeneous mixture stirred at room temperature for 45 minutes. The mixture was filtered, and the filtrate concentrated to give a yellow foam. This foam was purified by column chromatography using flash silica eluting with dichloromethane:methanol (10:1) to give the title product (0.133g) as a yellow foam. MH^+=615, ^1H nmr δ (DMSO-d_6) includes 1.00-1.12 (m,3H), 3.98-4.70 (m,4H), 5.56-5.96 (m,3H), 7.10-7.40 (m,10H), 8.07-8.20 (m,1H), 8.36 (bs,1H).

INTERMEDIATE 28

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide

Triethylamine (4.8ml), bis(triphenylphosphine)palladium(II) chloride (0.016g) and copper(I)iodide (0.0011g) were added to a solution of 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (Intermediate 18, 0.750g) in anhydrous DMF (32ml) and anhydrous acetonitrile (64ml). The mixture was treated with 3-(piperidin-1-yl)propyne (Intermediate 19, 0.705g) , then stirred at room temperature for 40 hours. Dichloromethane (250ml) and water (50ml) were added and the phases separated. The aqueous phase was further extracted with dichloromethane (2x70ml), then the extracts were combined, washed with brine (250ml), dried ($MgSO_4$) and concentrated to give a yellow foam. This foam was purified by column chromatography on flash silica eluting with dichloromethane:methanol (25:1) to give the title product (0.488g) as a brown solid. MH^+=650, ^1H nmr δ (DMSO-d_6) includes 0.60 (t,3H), 1.25-1.40 (m,5H), 1.40-1.58 (m,7H), 2.23 (t,4H), 2.70-2.90 (m,2H), 3.45 (bs,2H), 3.95-4.06 (hump, 2H), 4.45-4.60 (m,2H), 5.28-5.35 (bs,2H), 6.24 (bs,1H), 7.10-7.30 (m,10H), 7.42-7.52 (m,1H), 7.88-7.96 (m,1H), 8.20 (s,1H).

EXAMPLE 1

1-[2-Cyclohexylthio-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

Cyclohexanethiol (138 µl) was added to a stirred suspension of sodium hydride (60%, 45mg) in DMF (2ml) under nitrogen. After 1h at room temperature 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 63mg) was added and the mixture heated to 95° for 3h. On cooling, the reaction mixture was diluted with ethyl acetate (75ml) and washed with 0.05M hydrochloric acid (50ml), water (2x50ml) and brine (50ml). The organic phase was dried ($MgSO_4$) and evaporated to give a gum which was purified on flash silica. Elution with methanol: chloroform (1:19 → 1:9) afforded the title compound as a white solid (49mg). MH^+ = 603; ^1H nmr δ (DMSO-d_6) includes 3.77 (m, 1H), 4.07 - 4.17 (m, 3H), 4.28 (s,1H), 4.50 - 4.67 (m, 2H), 5.53 (d, 1H) 5.69 (d, 1H), 5.86 (d, 1H), 7.14 - 7.38 (m,10H), 8.1 (brt, 1H), 8.23 (s, 1H), 8.32 (brt, 1H).

EXAMPLE 2

(cis)-1-[2-[(4-Aminocyclohexyl)thio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide.

A stirred solution of (cis)-[4-(acetylthio)cyclohexyl]carbamic acid 1,1-dimethylethyl ester (Intermediate 13, 147mg) in DMF (2ml) was treated with a solution of 1M aqueous sodium hydroxide (0.6ml) under nitrogen. After 0.5h at room temperature 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 150mg) was added and the mixture heated to 95° for 24h. On cooling, the reaction mixture was poured into ethyl acetate (200ml) and washed with water (3x100ml) and brine (100ml). The organic phase was dried ($MgSO_4$) and evaporated to give a gum (240mg) which was treated with trifluorocetic acid (2ml) and water (0.2ml). After stirring at room temperature for 15 min the mixture was evaporated and the residue dissolved in ethyl acetate (100ml) and washed with saturated sodium hydrogen carbonate solution (100ml). The aqueous phase was extracted with ethyl acetate (50ml) and the combined organic solutions were washed with water (2x100ml) and brine (100ml). The organic phase was dried ($MgSO_4$) and evaporated to give an orange foam which was purified on flash silica. Elution with dichloromethane: methanol: 0.88 aqueous ammonia (30:4:1) afforded the title compound as a white solid (53mg). MH^+ = 618; ^1H nmr δ (DMSO-d_6) includes 1.05 (t, 3H), 3.95 - 4.18 (m, 4H), 4.27 (s, 1H), 4.50 - 4.65 (m, 2H), 5.52 (brs, 1H), 5.68 (brs, 1H), 5.87 (d, 1H), 7.16 - 7.37 (m, 10H), 8.04 (m, 1H), 8.22 (s, 1H), 8.31 (m, 1H).

EXAMPLE 3

1-[2-(3-Aminophenylthio)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide

1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (Intermediate 9, 0.103g), 3-aminothiophenol (0.15ml) and potassium carbonate (0.03g) in DMSO (0.4ml) were stirred under nitrogen and heated at 140°C for 4h. The solution was added to water (50ml) and extracted with ethyl acetate (100ml then 50ml). The total organic solution was washed with water (10ml) th n dri d (Na_2SO_4)

vaporated and purified on flash silica (15g) eluting with dichloromethane : methanol (24:1) to give a pale brown foam (89mg).

The foam (85mg), trifluoroacetic acid (0.9ml) and water (0.1ml) were stirred at 20°C for 2.5h. The solution was evaporated to a gum (139mg) which was purified on flash silica (15g) eluting with dichloromethane : methanol (19:1) to give a gum (61mg). Further purification on flash silica (15g) eluting with ethyl acetate:ethanol (24:1) followed by ethyl acetate:dichloromethane:ethanol (10:10:2) gave the title compound (32mg) as an off-white solid. MH^+ = 612; ^1H nmr δ (DMSO-d_6) 1.08(t,3H), 3.13-3.4(m,2H), 3.85(m) and 4.11(m)(total 3H), 4.27(s,1H), 4.31(t,1H), 4.58(m,1H), 5.31(brs,2H), 5.53(d,1H), 5.70(d,1H), 5.85(d,1H), 6.68(d,1H), 6.84(d,1H), 6.95(s,1H), 7.02-7.36(m,11H), 8.0(t,1H), 8.22(s,1H), 8.39(t,1H).

EXAMPLE 4

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-2,3-O-(1-methylethylidene)-β-D-ribofuranuronamide (Intermediate 28, 0.430g) was treated with trifluoroacetic acid (7.2ml) followed by water (0.80ml), and stirred at room temperature for an hour. The mixture was concentrated and azeotroped three times with methanol to give the title compound associated with trifluoroacetic acid (0.490g) as a brown foam. MH^+=610, ^1H nmr δ (DMSO-d_6) includes 1.05 (t,3H), 1.56-1.96 (m,6H), 2.96-3.16 (m,2H), 3.16-3.26 (m,2H), 4.04-4.20 (m,3H), 4.32 (bs,1H), 4.41 (bs,1H), 4.50-4.62 (m,2H), 5.96 (d,1H), 7.16-7.40 (m,10H), 8.20-8.32 (m,1H), 8.33-8.42 (m,1H), 8.54 (s,1H).

EXAMPLE 5

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)propyl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide (Example 4, 0.050g) in ethanol (5ml) was added to palladium on charcoal (10%, 0.0015g) which had be n pr -treated with water (0.50ml), and this mixture stirred under hydrogen for fiv days. The

solution was filtered through a pad of celite, the residue washed with ethanol, and the filtrate and washings then combined and evaporated to give a yellow oil. This oil was purified by preparative high pressure liquid chromatography on an ODS-2 column eluting with a gradient mixture of acetonitrile:water, acidified with 0.8ml per litre of trifluoroacetic acid, to give the title compound associated with trifluoroacetic acid (0.042g) as a brown foam. MH^+=614, ^1H nmr δ (DMSO-d_6) includes 1.02 (t,3H), 1.55-1.85 (m,6H), 2.10-2.25 (m,2H), 2.78-2.90 (m,4H), 3.10-3.25 (m,4H), 4.30 (bs,1H), 4.58-4.66 (m,2H), 5.98 (d,1H), 7.15-7.40 (m,10H), 7.90-8.05 (hump,1H), 8.27-8.36 (hump,1H), 8.39 (bs,1H).

EXAMPLE 6

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-E-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide (Example 4, , 0.050g) in ethanol (1.5ml) was added to palladium on calcium carbonate, poisoned with lead (5%, 0.020g) which had been pre-treated with water (0.25ml), and the mixture stirred under hydrogen for seven days. The solution was filtered through a pad of celite, the residue washed with ethanol, and the filtrate and washings then combined and evaporated to give a brown solid. This solid was purified by preparative thin layer chromatography using a normal phase silica gel plate eluting with dichloromethane:methanol (5:1) to give the title compound (0.010g) as a pale yellow solid. MH^+=612, ^1H nmr δ (DMSO-d_6) includes 1.02 (t,3H), 1.60-1.80 (m,6H), 2.70-2.82 (m,2H), 3.35-3.45 (m,2H), 4.22-4.30 (m,2H), 4.27 (dd,1H), 4.53-4.60 (m,3H), 4.66 (dd,1H), 6.01 (d,1H), 6.08 (dt,1H), 6.66 (dt,1H), 7.16-7.36 (m,10H), 8.43 (bs,1H).

EXAMPLE 7

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-Z-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A mixture of 1-deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-iodo-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide (Intermediate 27, - 0.080g), bis(triphenylphosphine)palladium(II) chloride (0.0046g) and [3-Z-(piperidin-1-yl)-1-propene-1-yl]tri-*n*-butyltin (Intermediate 22, 0.122g) in dry dimethylformamide (1ml) was heated with stirring at 120°C for 48 hours. It was then allowed to cool, and

concentrated to give a brown liquid. This liquid was treated with a saturated solution of potassium fluoride in methanol (15ml) and the mixture stirred for four hours. The mixture was concentrated and the purification of the resulting brown residue was attempted once by column chromatography on flash silica eluting with dichloromethane:methanol(20:1), once using preparative high pressure liquid chromatography on an ODS-2 column eluting with a gradient mixture of acetonitrile:water,then acetonitrile:water acidified with 0.8ml per litre of trifluoroacetic acid, and once by preparative thin layer chromatography using a normal phase silica gel plate eluting with dichloromethane:methanol (5:1). The mixture was then successfully purified by preparative thin layer chromatography using a normal phase silica gel plate eluting twice with dichloromethane:methanol (5:1) to give the title product associated with trifluoroacetic acid (0.005g) as a white solid. MH^+=612, ^1H nmr δ (CD_3OD) includes 1.10 (t,3H), 1.50-1.82 (m,6H), 2.78-3.08 (humps,4H), 3.20-3.38 (m,2H), 4.26-4.34 (hump,2H), 4.40-4.55 (m,5H), 6.04-6.12 (m,2H), 6.71 (d,1H), 7.16-7.36 (m,10H), 8.35 (bs,1H).

EXAMPLE 8

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.25g) was added in portions to a stirred solution of 2-(piperidin-1-yl)ethanol (2ml,) in dimethoxyethane (5 ml) under nitrogen. When effervescence had ceased 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.25g) was added and the mixture was heated under nitrogen at 55° C for 24h. The cooled reaction was partitioned between ethyl acetate (50 ml) and water (50 ml). The organic phase was washed with water (2x30ml), dried ($MgSO_4$) and evaporated to leave an oil which was stirred with cyclohexane (20ml) for 2h. The resulting solid was collected by filtration and purified by column chromatography on flash silica eluted with dichloromethane:ethanol:0.88ammonia (100:8:1) to give the title compound (93mg) as a solid from ether. MH^+=616, ^1H nmr δ (DMSO-d_6) includes 1.05 (t,3H), 1.38 (m,2H), 1.48 (m,4H), 2.42 (m,4H), 2.67 (t,2H), 3.25 (m,2H), 4.08 (m,3H), 4.26 (bs,1H), 4.45 (t,2H), 4.53 (q,1H), 4.64 (t,1H), 5.47 (d,1H), 5.72 (d,1H), 5.83 (d,1H), 7.1-7.4 (m,10H), 8.1 (m,2H), 9.15 (t,1H).

EXAMPLE 9

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.2g) was added to a stirred solution of 2-(morpholin-4-yl)ethanol (2.5g) in dimethoxyethane (5ml) under nitrogen. When effervescence had ceased 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.23g) was added and the reaction heated at 55° C for 18h. The cooled mixture was diluted with water (30ml) and extracted into ethyl acetate (30ml, 20ml). The extract was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica gradiently eluted with dichloromethane to 7.5% methanol in dichloromethane to give the title compound (0.103g) as a solid from ether. MH^+ = 618, ^1H nmr δ (DMSO-d_6) includes 1.03 (t,3H), 2.42 (m,4H), 2.7 (t,2H), 3.25 (m,2H), 3.55 (4H), 4.1 (m,3H), 4.25 (s,1H), 4.38-4.7 (m,3H), 5.5 (d,1H), 5.75 (d,1H), 5.8 (d,1H), 7.1-7.4 (m,10H), 8.1 (s,1H), 8.12 (m,1H), 9.2 (m,1H).

EXAMPLE 10

1-Deoxy-1-[2-[2-(dimethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.2g) was added to a stirred solution of 2-(dimethylamino)ethanol (2.7g) in dimethoxyethane (3ml) under nitrogen. When effervescence had ceased 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.23g) was added and the reaction heated at 55° C for 18h. The cooled mixture was diluted with water (70ml) and extracted into ethyl acetate (2 x 30ml). The extract was washed with water (30ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica gradiently eluted with dichloromethane to dichloromethane: ethanol: 0.88 ammonia (50:5:1) to give the title compound (0.130g) as a solid from ether. MH^+ = 576, ^1H nmr δ (DMSO-d_6) includes 1.02 (t,3H), 2.22 (s,6H), 3.65 (t,2H), 3.25 (m,2H), 4.1 (m,3H), 4.25 (bs,1H), 4.45 (m,2H), 4.55(q,1H), 4.62 (t,1H), 5.5 (d,1H), 5.72 (d,1H), 6.82 (d,1H), 7.1-7.4 (10H), 8.12 (s,1H), 8.14 (m,1H), 9.2 (m,1H).

EXAMPLE 11

1-Deoxy-1-[2-[2-(diethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.2g) was added to a stirred solution of 2-(diethylamino)ethanol (3.0g) in dimethoxyethane (3ml) under nitrogen. When effervescence had ceased 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.236g) was added and the reaction heated at 55° C for 18h. The cooled mixture was diluted with water (50ml) and extracted into ethyl acetate (3 x 30ml). The extract was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica eluted with dichloromethane: ethanol: 0.88 ammonia (50:5:1) to give the title compound (0.063g) as a solid from ether. MH^+ = 604, ^1H nmr δ (DMSO-d_6) includes 0.95 (t,3H), 1.06 (t,3H), ~2.55 (m,4H), 2.78 (m,2H), 3.25 (m,2H), 4.08 (m,3H), 4.27 (bs,1H), 4.42 (m,2H), 4.54 (q,1H), 4.65 (t,1H), 5.49 (d,1H), 5.73 (d,1H), 5.83 (d,1H), 7.15-7.4 (m,10H), 8.12 (bs,1H), 8.14 (t,1H), 9.16 (hump,1H).

EXAMPLE 12

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.2g) was added to a stirred solution of 2-(pyrrolidin-1-yl)ethanol (2.7g) in dimethoxyethane (3ml) under nitrogen. When effervescence had ceased 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.23g) was added and the reaction heated at 55° C for 18h. The cooled mixture was diluted with water (50ml) and extracted into ethyl acetate (30ml, 20ml). The extract was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave an oil which was purified by column chromatography on flash silica gradiently eluted with dichloromethane to dichloromethane: ethanol: 0.88 ammonia (50:5:1) to give the title compound (0.089g) as a solid from ether. MH^+ = 602, ^1H nmr δ (DMSO-d_6) includes 1.02 (t,3H), 1.32 (m,4H), 2.8 (t,2H), 3.05-3.15 (m,2H), 4.1 (m,3H), 4.22 (s,1H), 4.42 (m,1H), 4.45 (m,1H), 4.62 (t,2H), 5.62 (d,1H), 5.7 (d,1H), 5.81 (d,1H), 7.1-7.3 (m,10H), 8.1 (s,1H), 8.12 (t,1H), 9.1 (t,1H).

EXAMPLE 13

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.1g) was added in portions to methanol (10ml) under nitrogen. When effervescence had ceased the methanol was removed and DMF (3ml) added followed immediately by a solution of acetic acid 2-(piperidin-1-yl)ethylthio ester (Intermediate 23, 0.55g) in DMF (1ml). The mixture was stirred under nitrogen for 0.75h then 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.25g) was added. The reaction was stirred under nitrogen for 48h, diluted with water (50ml) and extracted into ethyl acetate (3x30ml). The extract was washed with water (2x20ml), dried ($MgSO_4$) and evaporated to leave an oil which was subjected to column chromatography on flash silica eluted with dichloromethane:ethanol:0.88ammonia (100:8:1) to give an oil which provided the title compound (0.201g) as a solid on treatment with ether. MH^+ = 632, ^1H nmr δ (DMSO-d_6) includes 1.05 (t,3H), 1.35 (m,2H), 1.44 (4H), 2.39 (m,4H), 2.65 (m,2H), 3.23 (m,2H), 4.15 (m,3H), 4.28 (s,1H), 4.6 (m,2H), 5.51 (d,1H), 5.67 (d,1H), 5.87 (d,1H), 7.1-7.4 (m,10H), 8.01 (t, 1H), 8.24 (s,1H), 8.29 (t,1H).

EXAMPLE 14

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

A solution of 2-(morpholin-4-yl)ethanethiol (0.7g) in DMF (8ml) was stirred under nitrogen with 60% oil dispersed sodium hydride (0.142g) until effervescence ceased. 1-[2-Chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.2g) was then added to give a yellow solution which was stirred for 18h. Water (120ml) was added and the product was extracted into ethyl acetate (3x50ml). The extract was washed with water (50ml), dried ($MgSO_4$) and evaporated to low bulk before applying to the top of a flash silica column and the title compound (0.155g) obtained by elution with ethyl acetate and evaporation to a solid . MH^+ = 634, ^1H nmr δ (DMSO-d_6) includes 1.03 (t,3H), 2.38 (m,4H), 2.62 (t,2H), 3.25 (m,2H), 3.5 (m,4H), 4.12 (m,3H), 4.28 (s,1H), 4.58 (m,2H), 5.55 (d,1H), 5.7 (d,1H), 6.85 (d,1H), 7.1-7.4 (m,10H), 8.07 (t,1H), 8.25 (s,1H), 8.33 (t,1H).

EXAMPLE 15

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.1g) was added in portions to a solution of acetic acid 2-(pyrrolidin-1-yl)ethylthio ester (Intermediate 24, 0.495g) in methanol (5ml) under nitrogen. When effervescence had ceased the mixture was left for 0.75h before 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.25g) was added. The reaction was stirred under nitrogen for 18h, the methanol was removed and then DMF (2ml) was added. More 60% oil dispersed sodium hydride (0.05g) was added and the reaction stirred for a further 3 days. Water (50ml) was added and the precipitate was extracted into ethyl acetate (3x30ml). The extract was washed with water (30ml), dried ($MgSO_4$) and evaporated to leave an oil which was subjected to column chromatography on flash silica eluted with dichloromethane:ethanol:0.88ammonia (100:8:1) to give an oil. This was dissolved in dichloromethane: ethanol (200:1) and the solution was filtered. The filtrate was evaporated to give an oil which provided the title compound (0.085g) as a solid on treatment with ether. MH^+ = 632, ^1H nmr δ (DMSO-d_6) includes 1.04 (t,3H), 1.65 (m,4H), 2.68 (dd,1H), 2.78 (t,2H), 2.86 (dd,1H), 3.22 (m,2H), 4.15 (m,3H), 4.27 (d,1H), 4.6 (m,2H), 5.49 (d,1H), 5.66 (m,1H), 5.87 (d,1H), 7.1-7.4 (m,10H), 8.0 (t,1H), 8.2-8.3 (m,2H).

EXAMPLE 16

1-Deoxy-1-[2-[2-(diethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

60% Oil dispersed sodium hydride (0.1g) was added in portions to methanol (10ml) under nitrogen. When effervescence had ceased the methanol was removed and a solution of acetic acid 2-(diethylamino)ethylthio ester (Intermediate 25, 0.70g) in DMF (3ml) was added. The mixture was stirred under nitrogen for 0.75h then 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.253g) was added. After stirring under nitrogen for 18h, the reaction was diluted with water (50ml) and extracted into ethyl acetate (2 x 30ml). The extract was washed with water (20ml), dried ($MgSO_4$) and evaporated to leave an oil which was subjected to

column chromatography on flash silica eluted with dichloromethane:ethanol:0.88 ammonia (100:8:1) to give an oil which provided the title compound (0.221g) as a solid on treatment with ether. MH^+ = 620, ^1H nmr δ (DMSO-d_6) includes 0.92 (t,6H), 1.05 (t,3H), 2.73 (m,2H), 3.23 (m,4H), 4.12 (m,3H), 4.27 (d,1H), 4.59 (m,2H), 5.51 (d,1H), 5.66 (d,1H), 5.89 (d,1H), 7.1-7.4 (m,10H), 802 (t,1H), 8.24 (bs,1H), 8.3 (t,1H).

EXAMPLE 17

1-Deoxy-1-[2-[2-(dimethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide

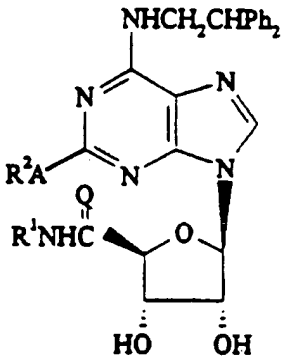
60% Oil dispersed sodium hydride (0.1g) was added in portions to methanol (10ml) under nitrogen. When effervescence had ceased the methanol was removed and a solution of acetic acid 2-(dimethylamino)ethylthio ester (Intermediate 26, 0.44g) in DMF (3ml) was added. The mixture was stirred under nitrogen for 0.75h then 1-[2-chloro-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide (Intermediate 10, 0.242g) was added. After stirring under nitrogen for 48h, the reaction was diluted with water (50ml) and extracted into ethyl acetate (2 x 20ml). The extract was washed with water (30ml), dried ($MgSO_4$) and evaporated to leave a gelatinous solid which was subjected to column chromatography on flash silica eluted with dichloromethane:ethanol:0.88 ammonia (100:8:1) to give an oil which provided the title compound (0.221g) as a solid on treatment with ether. MH^+ = 592, ^1H nmr δ (DMSO-d_6) includes 1.04 (t,3H), 2.17 (s,6H), 2.58 (t,2H), 3.22 (m,2H), 4.15 (m,3H), 4.28 (d,1H), 4.58 (m,2H), 5.49 (d,1H), 5.64 (bs,1H), 5.88 (d,1H), 7.1-7.4 (m,10H), 8.0 (t,1H), 8.2-8.3 (m,2H).

The effects of compounds of the invention on fMLP activation of O_2^--generation

The potential for compounds of formula (I) to inhibit leukocyte function was examined by measuring the ability of the compounds to inhibit superoxide (O_2^-) generation from neutrophils stimulated with fMLP following the procedure described by W. Busse et al. in J Allergy Clin. Immunology, 83(2) Part 1, 400-405 (1989). Thus, for example, compounds of Examples 4 to 17 were more active than NECA with some compounds being more than 50 times more potent than NECA in this study.

CLAIMS

1. A compound of general formula (I)



(I)

and salts and solvates thereof, wherein:

R^1 represents a hydrogen atom or a C_{3-6}cycloalkyl or C_{1-6}alkyl group;

A represents O, S, SO, SO_2, a saturated hydrocarbon moiety having from 1 to 4 carbon atoms or an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms;

R^2 represents a group selected from

(i) C_{3-8}cycloalkyl

(ii) C_{3-8}cycloalkyl substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p is zero or 1 and R^3 is hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino)

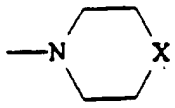
(iii) pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl)

(iv) pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl (e.g. benzyl) and one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(v) C_{3-8}cycloalkylC_{1-6}alkyl

(vi) C_{3-8}cycloalkylC_{1-6}alkyl in which one or more of the ring carbon atoms (e.g. 1, 2 or 3 ring carbon atoms) is substituted by the same or different groups selected from C_{2-7}acylamino, guanidino, carboxyl, oxo and $(CH_2)pR^3$ (where p and R^3 are as defined previously)

(vii) $-Alk_1Y$ where Alk_1 is a C_{2-6} alkylene group or a bond and Y is a group selected from C_{2-7}acylamino, guanidino, hydroxyl, NH_2, C_{1-6}alkylamino, diC_{1-6}alkylamino or



(where X is a bond, O, CH_2 or NR^4 in which R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl) and

(viii) $-(CHR^5)_m(Alk_2)_nZ$ where m and n each independently represent zero or 1 except that when m is 1 then n must also represent 1, R^5 is a hydrogen atom or a carboxy group or a group CH_2R^6 (where R^6 is C_{2-7}acylamino, guanidino, hydroxy, methoxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino), Alk_2 is a C_{1-5}alkylidene group and Z is a hydrogen atom or an optionally substituted aromatic ring selected from phenyl, pyridyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl and benzimidazolyl where the ring is optionally substituted by one or more groups (e.g. 1, 2 or 3 groups) which may be the same or different and are selected from C_{1-6}alkyl, C_{2-7}acylamino, guanidino, carboxyC_{1-4}alkyl, hydroxy, NH_2, C_{1-6}alkylamino or diC_{1-6}alkylamino;

Q represents an oxygen or sulphur atom; and

Ph represents phenyl;

with the proviso that when A represents O, S, SO or SO_2, Alk_1 represents a C_{2-6}alkylene group.

2. A compound according to claim 1 in which R^1 is C_{1-3} alkyl.

3. A compound according to claim 1 or claim 2 in which Q is an oxygen atom.

4. A compound according to claim 1 in which $R^1NHC(=Q)-$ is ethylaminocarbonyl.

5. A compound according to any of claims 1 to 4 in which A represents a sulphur atom.

6. A compound according to any of claims 1 to 4 in which A represents an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms.

7. A compound according to any preceding claim in which R^2 is cyclopentyl or cyclohexyl each substituted by one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino, acetamido or trifluoroacetamido.

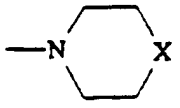
8. A compound according to claim 7 in which R^2 is cyclopentyl or cyclohexyl each substituted by one or two groups selected from hydroxy, NH_2, methylamino, dimethylamino.

9. A compound according to any of claims 1 to 6 in which R^2 is pyrrolidin-3-yl or piperidin-3-yl in which the ring nitrogen atom is substituted by hydrogen, C_{1-3}alkyl or benzyl.

10. A compound according to any of claims 1 to 6 in which R^2 represents $(CHR^5)_m$ $(Alk2)_nZ$ where R^5, m and n are as defined previously and Z is an optionally substituted imidazolyl, 1-pyrrolidinyl or 1-piperidinyl group.

11. A compound according to claim 10 in which $-(CHR^5)_m(Alk_2)_n-$ is $-CH_2CH_2-$.

12. A compound according to any of claims 1 to 6 in which R^2 is -Alk Y where Alk_1 is C_{2-6} alkylene group and Y is C_{1-6}alkylamino, diC_{1-6} alkylamino or



(where X is a bond, 0 or CH_2).

13. 1-[2-Cyclohexylthio-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

(cis)-1-[2-[(4-Aminocyclohexyl)thio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

1-[2-(3-Aminophenylthio)-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)propyl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-E-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-Z-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[2-[2-(dimethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[2-[2-(diethylamino)ethoxy]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethoxy]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(morpholin-4-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(pyrrolidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[2-[2-(diethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

1-Deoxy-1-[2-[2-(dimethylamino)ethylthio]-6-[(2,2-diphenylethyl)amino]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide;

and physiologically acceptable salts and solvates thereof.

14. 1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[2-(piperidin-1-yl)ethylthio]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide and physiologically acceptable salts and solvates thereof.

15. 1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-E-(piperidin-1-yl)-1-propen-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide and physiologically acceptable salts and solvates thereof.

16. 1-Deoxy-1-[6-[(2,2-diphenylethyl)amino]-2-[3-(piperidin-1-yl)-1-propyn-1-yl]-9H-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide and physiologically acceptable salts and solvates thereof.

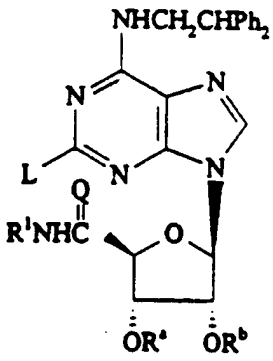
17. A compound of formula (I) as defined in any preceding claim for use in human or veterinary medicine.

18. Use of a compound of formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment of patients with inflammatory conditions with are susceptible to leukocyte-induced tissue damage.

19. A pharmaceutical composition comprising a compound of formula (I) as defined in any preceding claim together if desirable, with one or more physiologically acceptable carriers or excipients.

20. A process for the preparation of a compound of formula (I) as defined in claim 1, which comprises.

(A) treating a compound of formula (II)



(II)

(wherein L represents halo and R^a and R^b are each hydrogen or together form an alkylidene group) with a thiol $R^{2a}SH$ or a thiolate anion $R^{2a}S^-$ (wherein R^{2a} is a group R^2 or is a protected derivative thereof) followed, where necessary, by the removal of any protecting groups present; or

treating a compound of formula (II) above with an alkoxide $R^{2a}O^-$ (wherein R^{2a} is as previously defined), followed where necessary, by removal of any protecting groups present; or

treating a compound of formula (II) above with a terminal acetylene $R^{2a}A^aH$ (wherein R^{2a} is as previously defined, A^a represents a C_{1-4} hydrocarbon moiety and R^2A^aH contains a terminal triple bond) in the presence of a palladium (0) catalyst, followed where necessary by removal of any protecting groups present; or

treating a compound of formula (II) above with an alkylating agent in the presence of a palladium (0) catalyst, followed where necessary by removal of any protecting groups present; or

(B) deprotecting a protected derivative of a compound of formula (I), if necessary or desirable followed by (i) salt formulation or (ii) conversion of a compound of formula (I) to a different compound of formula (I) or (iii) preparation of an individual isomer of a compound of formula (I).

21. A method for the treatment of a human or animal subject with an inflammatory condition which is susceptible to leukocyte-induced tissue damage, which method comprises administering to said subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

22. Compounds according to any of Claims 1 to 16 substantially as herein described.

23. Compositions according to claim 19 substantially as herein described.

24. A process for the pr paration of a compound according to claim 1, the process substantially as herein described and exemplified.

PCT WORLD INTELLECTUAL PROPERTY International Bureau

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(74) Agents: DAWSON, Hugh, B. et al.; Glaxo Wellcome plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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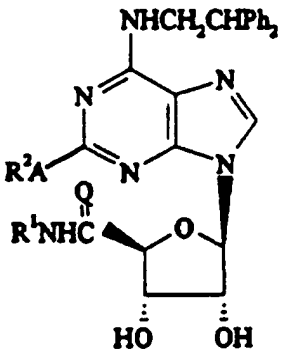
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 7 March 1996 (07.03.96)

(54) Title: AMINO PURINE-β-D-RIBOFURANURONAMIDE DERIVATIVES

(57) Abstract

Amino purine-β-D-ribofuranuronamide derivatives are described having general formula (I) and salts and solvates thereof, wherein: R^1 is hydrogen, C_{3-8}cycloaklyl or C_{1-6}alkyl; A represents O, S, SO, SO_2, a saturated hydrocarbon moiety having from 1 to 4 carbon atoms or an unsaturated hydrocarbon moiety having from 2 to 4 carbon atoms; R^2 is C_{3-8}cycloalkyl, C_{3-8}cycloalkyl C_{1-6}alkyl, Alk_1Y, $-(CHR^5)_m$ $(Alk2)_nZ$ or appropriately substituted C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-6}alkyl, pyrrolidin-3-yl, 2-oxopyrrolidin-4-yl, 2-oxopyrrolidin-5-yl, piperidin-3-yl or piperidin-4-yl, and Q is oxygen or sulphur with the proviso that when A represents O, S, SO or SO_2, Alk_1 represents a C_{2-6}alkylene group. Compounds of formula (I) and their salts and solvates have use in medicine as anti-inflammatory agents, particularly in the treatment of patients with inflammatory conditions who are susceptible to leukocyte-induced tissue damage.



(I)

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INTERNATIONAL SEARCH REPORT

International Application No
PC1/EP 95/02337

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H19/167 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,88 03147 (WARNER-LAMBERT COMPANY) 5 May 1988 see claims ---	1,17-19
Y	EP,A,0 222 330 (WARNER-LAMBERT COMPANY) 20 May 1987 see page 8 - page 12; example 3 ---	1,17-19
Y	EP,A,0 277 917 (CIBA-GEIGY AG) 10 August 1988 see page 2; claims --- -/--	1,17-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 1995	16. 01. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Day, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, 1992 WASHINGTON US, pages 2363-2368, CRISTALLI G. ET AL '2-Alkynyl Derivatives of Adenosine and Adenosine-5'-N-ethyluronamide as Selective Agonists of A2 Adenosine Receptors' see the whole document	1,17-19
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, 1990 WASHINGTON US, pages 1919-1924, HUTCHINSON A.J. ET AL '2-(Arylalkylamino)adenosine-5'-uronamides : A New Class of Highly Selective Adenosine A2 Receptor Ligands' see the whole document	1,17-19
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, 1992 WASHINGTON US, pages 1667-1673, TRIVEDI B.K. AND BRUNS R.F. 'C2,N6-Disubstituted Adenosines: Synthesis and Structure-Activity Relationships' see the whole document	1,17-19
Y	AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, vol. 9, 1993 pages 179-185, WOLLNER A ET AL 'Acting via A2 Receptors, Adenosine Inhibits the Upregulation of Mac-1 (CD11b/CD18) Expression on FMLP-stimulated Neutrophils' see the whole document	1,17-19
Y	JOURNAL OF APPLIED PHYSIOLOGY, vol. 76, no. 1, January 1994 pages 5-13, CRONSTEIN B.N. 'Adenosine, an endogenous anti-inflammatory agent' see the whole document	1,17-19

1

INTERNATIONAL SEARCH REPORT

Inte ·ional application No.
PCT/EP 95/02837

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PC./EP 95/02837

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8803147	05-05-88	AU-B-	8276187	25-05-88
EP-A-222330	20-05-87	US-A-	4738954	19-04-88
		JP-A-	62111996	22-05-87
		US-A-	4868160	19-09-89
EP-A-277917	10-08-88	AU-B-	1123388	18-08-88
		JP-A-	63201196	19-08-88
		US-A-	4968697	06-11-90